

### **REMARKS**

The Office Action of September 2, 2005 presents the examination of pending claims 21-26. Claims 1-3, 5-8, 10, 11 and 13-20 are also pending but are withdrawn from consideration following restriction of the claims.

The claims are not amended by the present paper.

Applicants submit that, should the present claims 21-26 be found allowable, at least the withdrawn claims 11 and 13-20, being "product of making" claims which are commensurate in scope with the product claims 21-26, should be rejoined to the present application and allowed. MPEP 804.21.

### **Interview**

An interview with the Examiner and her supervisor was held on November 29, 2005. Applicants wish to thank the Examiner and her supervisor for their time and the effort expended to advance the prosecution of this application. The substance of the interview is explained further by the remarks hereinbelow.

### **Rejections over prior art**

Claims 21 and 23-26 stand rejected under 35 U.S.C. § 102(b) as lacking novelty over Yamamura, Cantrell or Yarkoni. Claims 21-26 stand rejected under 35 U.S.C. § 102(b) as lacking novelty over Van Nest. Claims 21, 23, 24 and 26 are newly rejected under 35 U.S.C. § 102(b) as lacking novelty over Zbar et al. All of these rejections are respectfully traversed. Reconsideration and withdrawal thereof are requested.

The present claims 21-26 are written in product-by-process terms. The Examiner has correctly stated Applicants' legal burden, which is to demonstrate by a preponderance of the evidence that the process steps recited in the claims provide some result that is distinct from the

processes disclosed in the references. Applicants submit that the evidence of record is sufficient to meet this burden, and therefore the instant rejections should be withdrawn.

In the interview of November 29, Applicants' Representative argued that, contrary to the assertions of the Examiner, the prior art does not disclose or suggest that an organic solvent should be used during the preparation of an emulsion of the BCG-CWS. That is, all of the prior art references cited disclose that the BCG-CWS should be dispersed in an oil, and then the dispersion should be emulsified with an aqueous solution of a detergent of some sort. On the other hand, the present claims recite a process in which the BCG-CWS is dispersed in an oil and an organic solvent before the dispersion is then emulsified in an aqueous solution. See, e.g., step a) of claim 21.

As has been argued previously, the evidence shown by the Kawabe Declaration and the Nomura Declarations I and II of record show that including a solvent in the step of dispersing the BCG-CWS in the oil provides an emulsion having a more uniform particle size that lacks any large aggregates. The evidence further shows that a consequence of this is that the resulting emulsions are more stable compared to emulsions prepared by dispersing the BCG-CWS in an oil without an organic solvent prior to emulsification, as is done in each of the references cited by the Examiner. The Kawabe Declaration further shows that exposing the BCG-CWS to the solvent, rather than to an aqueous environment, results in a different morphology of this reagent that exposes different chemical moieties to the solvent and this may be at least a part of the physical basis for the difference in the result. All of these conclusions are readily evident by visual inspection of the photographs that are a part of these declarations of record.

In the interview, the Examiner and her supervisor seemed inclined to agree that the evidence of the Kawabe and Nomura Declarations I and II is persuasive, but reserved final comment. It was made clear in the interview that the copies of the declarations that the Examiner had in the file did not clearly show the photographs included in the declarations, and thus critical aspects of the evidence were not able to be seen. Accordingly, Applicants' Representative left the Examiner with clearer copies of the declarations for the USPTO file.

In the interview, the Examiner had a question of how the particle size was determined in the experiments described in the specification and in the declarations. In the experiments shown in the present specification, the average particle diameter and particle size distribution were determined by a laser diffraction particle size analyzer (SALD3000. Shimadzu Corp.), as described at page 15, lines 19-22 and page 29, line 16 to page 30, line 1. In the Nomura Declarations I, made of record June 29, 2004, the observation of particles composed of BCG-CWS encapsulated in squalane was conducted visually, using a microscope. Experiment 1, where a dispersion-aiding solvent was used, gave suspension of homogeneous microparticles of BCG-CWS/oil with no aggregation. It was confirmed that all the particles prepared using an organic solvent together with an oil for the dispersion step were smaller than 25  $\mu\text{m}$  in size by measuring with a SALD-3000 particle size analyzer. On the other hand, Experiment 2, in which no organic solvent (dispersion-aiding solvent) was used, gave a mixture containing some very large particles, with a particle size of 100  $\mu\text{m}$  or larger (See, page 5, Experiment 2). Such a very large particle cannot be measured with a device for measuring particle size distribution.

In the Nomura Declaration II, made of record on March 30, 2005, the particles in the emulsions obtained both in the presence and in the absence of an organic solvent (dispersion-aiding solvent) were examined visually with a microscope. As can be seen from Figs. 1 and 2 at page 4 and 5 of Nomura Declaration II, the emulsion obtained using an organic solvent together with an oil in the dispersion step contains homogeneous microparticles, while that obtained without using an organic solvent contains a huge mass due to aggregation or segregation.

In the interview, the relationship between the experiments of the working example 1.3 of the specification and the experiments described in the Nomura Declarations was also questioned. The basic procedures of the experiments in the Nomura Declarations I and II are the same as those in Example 1.3. The main difference in the experiments as described in the Nomura Declarations I and II from Example 11.3 is that 10% ethanol-90% heptane is used in place of toluene.

Details of the experimental procedures of the Nomura Declarations are provided below.

#### Experiment 1

For the preparation in which an organic solvent is used in the dispersion step, BCG-CWS (146.5 mg) as the bacterial cell wall component was added to a mixture of 32 g of squalane and 10 mL of 10% ethanol-90% heptane, and the resultant mixture was shaken or treated by ultrasonication at room temperature to perform the dispersion step. Then, the dispersion was heated at 60°C under a flow of nitrogen to evaporate the 10% ethanol-90% heptane. After that, 212 g of an aqueous solution of 0.02 %w/w Polysorbate 80/5.7% mannitol was added to the residue and rough emulsification was performed with a homomixer (CLEARMIX, 4600rpm for 5 min). Then the mixture was more completely emulsified (16000 rpm for 5 min) after addition of 1.8 g of 10 %w/w Polysorbate 80. Finally, 21.8 g of 10 %w/w Polysorbate 80 was added and emulsion was stirred at 4,600 rpm for 1 minute, thereby obtaining an oil-in-water emulsion.

In the case of the preparation without an organic solvent, a mixture of BCG-CWS and squalane was directly treated by ultrasonication in the dispersion step, then the emulsification procedure was as described above.

#### Experiment 2

For the preparation in which an organic solvent is used in the dispersion step, BCG-CWS (3 mg) as the bacterial cell wall component was added to a mixture of 50  $\mu$ L of squalane and 2 mL of 10% ethanol-90% heptane, and the resultant mixture was shaken or treated by ultrasonication at room temperature to perform the dispersion step. Then, the dispersion was heated at 60°C under a flow of nitrogen to evaporate the 10% ethanol-90% heptane. After that, 5 mL of an aqueous solution of 1 %w/w Polysorbate 80 was added to the residue and emulsification was performed with a Potter type homomixer (2000 rpm for 3 min).

For the preparation with an organic solvent, a mixture of BCG-CWS and squalane was treated by ultrasonication for the dispersion step, and then the dispersion was emulsified as described above.

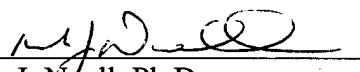
Applicants submit that none of the compositions described by Yamamura, Cantrell, Yarkoni, Van Nest or Zbar are prepared by a process in which a dispersion of the BCG-CWS is first made by mixing the BCG-CWS together with an oil and an organic solvent, then emulsifying the mixture. Thus, the process steps recited in the present claims 21-26, which include such a dispersion step, are distinct from the processes described in the references cited by the Examiner. Applicants have also made of record evidence sufficient to establish that this distinction in the process by which the compositions of the invention are made produces a more stable emulsion having a more uniform particle distribution that is free of aggregates and very large particles. Thus, the process features of the present "product-by-process" claims 21-26 in fact produce a product distinct from that described by Yamamura, Cantrell, Yarkoni, Van Nest and Zbar. Accordingly the standing rejections of the instant claims as lacking novelty over these references should be withdrawn.

Applicants submit that the present application well-describes and claims patentable subject matter. The favorable action of withdrawal of the standing rejections and passage of the application to issue are respectfully requested.

Should there be some minor issues remaining to be resolved that can be addressed by a telephone conversation, the Examiner is invited to telephone the undersigned at 703-205-8043 to discuss the matter.

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Respectfully submitted,

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